

AWARD NUMBER: W81XWH-12-2-0058

TITLE: Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy

PRINCIPAL INVESTIGATOR: Linda Cendales, MD

CONTRACTING ORGANIZATION: Duke University
Durham, NC 27705

REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2015		2. REPORT TYPE Annual Phase		3. DATES COVERED 30 Sep 2014 - 29 Sep 2015	
4. TITLE AND SUBTITLE Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-12-2-0058	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Linda Cendales, M.D. E-Mail: linda.cendales@dm.duke.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Duke University Medical Center 200 Trent Drive, Baker House Room 129 DUMC 3098 Durham, NC 27710				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The purpose of this study is to determine the safety and efficacy of hand transplantation as a treatment for patients with loss of limb below the elbow. The study will focus on patients who have had loss of limb. The primary endpoint is the ability to use the transplanted limb in activities of daily living at 18 months following transplantation measured by a quantitative functional test. Study activities include several study visits over 18 months and include; demographics, medical history, vital signs, psychosocial evaluation, urine, blood test, chest x-ray, bone density scans, and biopsies. Subjects who are 18-65 and willing to travel to site and have loss of limb will be included in study evaluation.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 4	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

Table of Contents

I. Introduction.....	4
II. Keywords.....	4
III. Accomplishments.....	4
IV. Impact.....	5
V. Changes/Problems.....	5
VI. Products.....	5
VII. Participants & Other Collaborating Organizations.....	6
VIII. Special Reporting Requirements.....	6
VIII. Appendices.....	6

I. Introduction

Recent improvements in body armor have reduced the rate of combat death but increased the rate of extremity injury, burn and limb loss in surviving casualties. As such, methods to replace injured limbs are increasingly required to support combat service personnel. Vascularized composite allotransplantation (VCA) has recently emerged as a promising strategy for the repair or replacement of amputated limbs, and novel methods for immune management to prevent the rejection of transplanted tissues are now available that may greatly reduce the risks associated with limb transplantation.

The proposal will utilize a comprehensive approach to efficiently apply the newest clinically proven methods of modulation of the immune system to lower the risk and improve the benefits of patients after limb reconstruction through transplantation. The study provides a new platform to optimize integration of a limb after limb loss with a therapy based on a once a month medication.

The entire study addresses the increase clinical need of limb loss seen in the current combat conflicts. The intervention provides the reconstruction of skin, muscle, tendon, bone, nerve, and vessels as a functional unit (limb) in individuals who suffered limb loss. The treatment includes the newest medication recently approved by the US Food and Drug Administration. Studies will define the efficacy of the newest medication on protective immunity and the mechanisms of graft rejection. Additionally, the studies will be conducted concurrently to determine in objective terms the integration of the recipients' use of their transplanted limb compared to their pre-transplant state. Moreover, evaluation of the recipient's quality of life will be performed.

II. Keywords

Clinical trial, amputation, hand transplant, rejection, clinical trial, Belatacept, vascularized composite allograft

III. Accomplishments

Regulatory Review and Approval Process

Our studies are under an Institutional Review Board (IRB) approved protocol entitled "Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy". The funding agency approved the submission of the protocol to the Duke Institutional Review Board on September 16, 2014. We received Duke's full institutional approval on November 14, 2014. The protocol was submitted to HRPO. The study was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, US Army, and USAMRMC human subjects protection requirements. The notification was received by the Principal Investigator on March 16, 2015.

After HRPO approval and]during this annual reporting period, we initiated the recruitment of potential candidates for limb transplantation. These process included recruitment letters, flyers, websites, and press releases. We distributed approved documents to DoD and Civilian centers nation-wide. This study was successfully registered on the clinicaltrials.gov website to comply with both institutional and federal guidelines (NCT02310867). During this study period no hand transplants were performed.

Site Visit

On November 3, 2014 a site visit from the funding agency was performed. The agenda included various presentations of various resources supporting the Duke Vascularized Composite Allotransplantation Program.

Other preparatory activities

- a) Two study initiation visits (SIV) and its accompanying training to the Duke Clinical Research Unit (DCRU) staff were conducted and documented by the PI and study support staff. The audience was both management and nursing staff within the Duke Clinical Research Unit (DCRU) who will be responsible for outpatient belatacept monthly infusions post-transplant.
- b) The training sessions were documented and can be found in the study regulatory binder.
- c) All case report forms from subject identification through 18 months post-transplant were vetted from both the PI and Duke Surgery Research Practices Manager.
- d) A query system, DEDUCE, created a report to capture potential subjects under a broad diagnosis within the Duke University Medical Center medical record system. The list was reviewed by the study team to select those who potentially fit both the study inclusion and exclusion criteria. Recruitment letters were sent to potential study candidates. PI and support staff conducted follow up telephone calls to those who were sent a recruitment letter.
- e) The PI and support staff performed a second screen of the potential candidates and send IRB and HRPO approved recruitment letters to the addresses on file.
- f) The PI continued conducting protocol specific training to the different multi-specialties involved in the procedure (e.g. rehabilitation, social work, operating room staff, organ procurement organization, etc.)
- g) An IRB amendment was approved to add website information about our Duke Hand Transplant Program to the Duke Medicine website (<https://www.dukemedicine.org/treatments/transplant-program/hand-transplant>)

IV. Impact

The results of this study will greatly aid decision making regarding ongoing and future cost-effective care of DoD casualties and veterans with limb injury and loss, potentially leading to improved rehabilitation, psychological adjustment, deployability, and reintegration to the community.

V. Changes/Problems

There have been no major changes to the protocol or field of study during this reporting year. The time of the administrative process has been a significant determinant on the study progress.

VI. Products

The 2015 annual report of the IND 113,206, Nulojix (Belatacept) was submitted to the FDA. Sponsor: Linda C. Cendales, MD

VII. Participants & Other Collaborating Organizations

There are no participant reports for this annual reporting period. There are also no collaborating organizations as this is a single-site study.

VIII. Special Reporting Requirements

There are no special reporting requirements to acknowledge for this annual reporting period.

IX. Appendices

Not applicable.